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Hyperbaric Oxygen in the Management of Osteoradionecrosis

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Hani Ashamalla, MD (Visiting Fellow, Radiation Oncology)

S.D. is an 8½-year-old white female who presented in late 1991 with a left earache and bleeding. An exophytic reddish mass was visualized in the external auditory meatus, with a palpable 1.5-cm jugulodigastric lymph node. Biopsy from the ear mass revealed embryonal rhabdomyosarcoma. Magnetic resonance imaging (MRI) of the brain showed an enhancing lesion of the left inner ear, extending to the mastoid with bony and intracranial extension. Cerebrospinal fluid (CSF) cytology was negative. Metastatic workup including chest computerized tomography (CT), bone marrow aspirate, and biopsy were also normal.

Dr. Winkler, would you please present the roentgen findings at the time of diagnosis?

Peter Winkler, MD (Neuroradiology Fellow)

The major findings were in the mastoid region of the left temporal bone (Fig. 1). The entire lateral portion of the temporal bone is filled with soft tissue without any mastoid air cells visible. The tumor extends to the middle ear cavity. Bone destruction or demineralization suggest an aggressive process. The child was not febrile, reducing the possibility of infection as an explanation for the findings. They are consistent, therefore, with a soft tissue tumor.

Antonia Uri, MD (Pediatric Pathologist)

This in fact is what was found. The sections of a biopsy specimen of the polypoid mass visualized in the external auditory canal show squamous epithelium with an underlying malignant neoplasm. The histologic appearance is that of an infiltrate of immature round cells with occasional pink cytoplasm. The neoplasm forms a typical cambium layer under the epithelium (Fig. 2). The desmin stain is positive, thus ruling out other "round cell tumors of childhood" such as neuroblastoma, lymphoma, and soft tissue Ewing sarcoma. The findings are those of an embryonal rhabdomyosarcoma. Neither the pattern nor the cytology of an alveolar rhabdomyosarcoma is detected in the sample.

Dr. Ashamalla. Multimodal therapy was initiated that included chemotherapy and radiation therapy. The chemotherapeutic agents were vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide. The schedule is intense and includes intrathecal chemotherapy using cytarabine, methotrexate, and hydrocortisone. External beam radiation therapy was added. Opposing fields to the whole brain were used initially, with 30 Gy in 150-cGy fractions administered over a period of 4 weeks. A smaller field was then employed to treat the left middle ear using 15 Mev photons and 20 Mev electrons to deliver an additional 2,520 cGy. The overall tumor dose was therefore, 5,520 cGy.

Pronounced side effects were encountered that included erythema and edema of the left external ear and auditory meatus, but the response of the tumor was excellent. By the completion of chemotherapy, she had no clear evidence of disease.

Follow-up over the next year following therapy was remarkable for a stenotic auditory canal which was refractory to surgical intervention. Neurocognitive evaluation performed on January 14, 1992 showed FSIQ to be 130. Disease evaluation demonstrated no evidence of progression. Repeated bouts of sinusitis were treated conservatively with antibiotics.

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Fig. 1. CT scan shows loss of mastoid air cells (dart) on the left, where a soft tissue mass fills the cavity and extends to the middle ear.

Dr. Winkler could you show us the studies obtained in the intervening time?

Dr. Winkler. The serial films are very interesting. Three and a half months after diagnosis when all treatment had been completed, the area of the left temporal bone that had been totally effaced now shows remineralization with coarse bony trabeculation (Fig. 3). All evidence of the soft tissue mass is gone.

Dr. Ashamalla. The patient fared well thereafter, but 2 years after diagnosis, she developed a bout of sinusitis and complained of pain in the ear. A CT scan was therefore obtained with some disturbing findings.

Dr. Winkler. The new CT scan shows a 1-cm defect in the area of bone that had been remineralized in the study 6 months before (Fig. 4). The differential diagnosis when confronted with such radiographic findings include infection, recurrent tumor, or necrosis. It is impossible roentgenographically to make the differentiation, of course, but absence of a visible soft tissue mass component would slightly favor bone necrosis rather than tumor recurrence.

Dr. Ashamalla. An open biopsy was obtained with no tumor being evident to the operating surgeon.

Dr. Uri. The specimen removed at that time is largely fibrous tissue that is focally chronically inflamed without there being any evidence of tumor. Small fragments of bone in the midst of nondescript fibrous tissue appear to be necrotic (Fig. 5).

Anna T. Meadows, MD (Pediatric Oncologist)

Was there something unusual about the radiation given to this child; for instance, is this a dose you commonly employ, Mr. Goldwein?

Joel Goldwein, MD (Pediatric Radiation Oncologist)

Yes, this is a dose that has been employed in many patients. It is conceivable that there had been pre-existing bone damage from the tumor, and that chemotherapy contributed to the intensity of the radiation effects.

Richard Womer, MD (Pediatric Oncologist)

The regimen used for her treatment includes intensive chemotherapy during the period of irradiation, and that might have been a factor.

Giulio J. D'Angio, MD (Pediatric Radiation Oncologist)

Patients who have chemotherapy-enhanced radiation reactions in deep tissues usually have evidence of this in the superficial structures as well, which therefore serve as a warning signal. Dr. Belasco, this child was your patient. Will you please describe the reaction mentioned earlier by Dr. Ashamalla?

Jean Belasco, MD (Pediatric Oncologist)

She developed a very brisk reaction in all the irradiated areas during treatment with swelling of the ear followed by desquamation of the pinna and retro-orbital skin. These tissues became both hemorrhagic and painful.

In any case, we were confronted with the findings of osteoradionecrosis, and prolonged discussion of management ensued. Some of our consultants felt that nothing more needed to be done, but Dr. Goldwein was of a different opinion.

Dr. Goldwein. Experience has shown that such foci of osteoradionecrosis are prone to infection, which can then lead to breakdown of the entire region. Since in this patient we were millimeters away from the meninges, it seemed wise to intervene at this point, and to promote healing in the region of the necrotic bone. Hyperbaric oxygen (HBO) has been found to promote healing in such cases, and it was therefore recommended to the parents that she undergo HBO therapy.

Dr. Ashamalla. The patient was referred for definitive HBO treatment of osteoradionecrosis. She underwent 31 dives at 2 atmospheres (66 feet of seawater), for 2 hours each from January 31, 1994 to March 18, 1994. The only side effect encountered was initial anxiety, and the patient has remained free of local problems since then.

Repeat CT scan of the head on March 21, 1994 showed some interesting new findings, which will be demonstrated by Dr. Winkler.

Dr. Winkler. The CT scan done a few days following completion of HBO therapy shows early remineralization

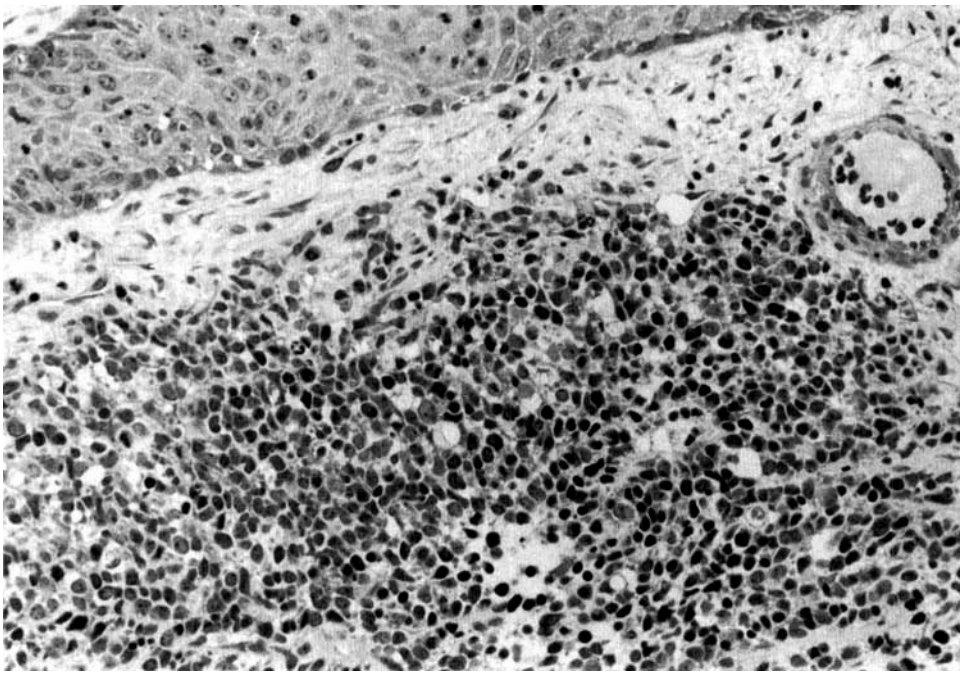

Fig. 2. Polypoid mass from the external auditory canal shows squamous epithelium with underlying infiltrate of embryonal rhabdomyosarcoma (hematoxylin-eosin, original magnification ×200).

Fig. 3. CT scan. Remineralization of the left mastoid is visible.

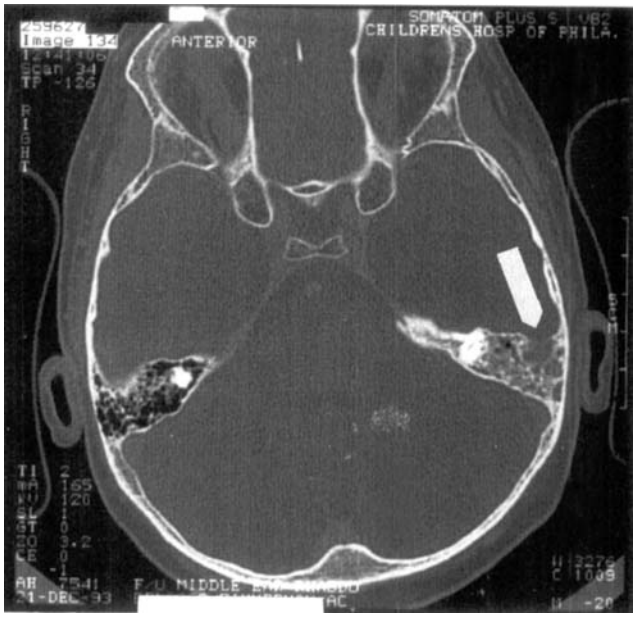

Fig. 4. CT scan. A 1-cm defect in the mastoid is present (dart) where mineralization had been present before (Fig. 3). The appearance favors bone necrosis (see text).

of the mastoid bone (Fig. 6). Moreover, aeration of the mastoid air cells is becoming apparent.

Dr. Goldwein. Dr. Ashamalla, would you please tell us why HBO helps in this setting.

Dr. Ashamalla. HBO works through two main mechanisms. The first is stimulation of angiogenesis, which was demonstrated by Myers and Marx in 1990 [1]. They compared serial transcutaneous (TcO_2) oxygen measurements in irradiated and non-irradiated tissue in patients breathing first room air and later, HBO that same day. By day 22, the TcO_2 in irradiated tissue had risen from a day

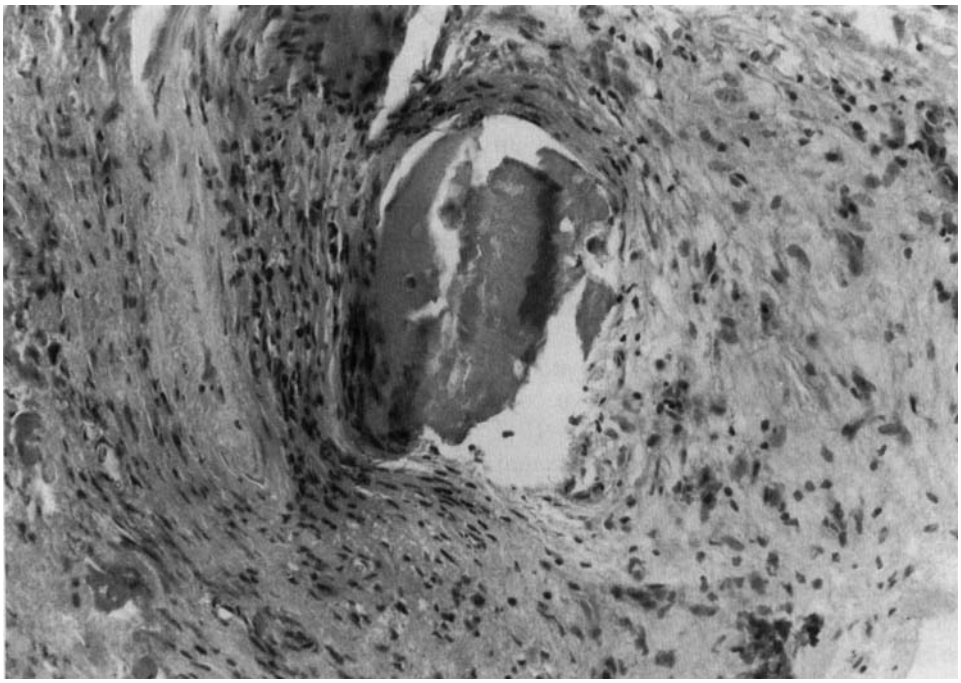

Fig. 5. Post-therapy tissue from the mastoid shows devitalized bone surrounded by granulation tissue. No evidence of tumor (hematoxylin-eosin, original magnification ×200).

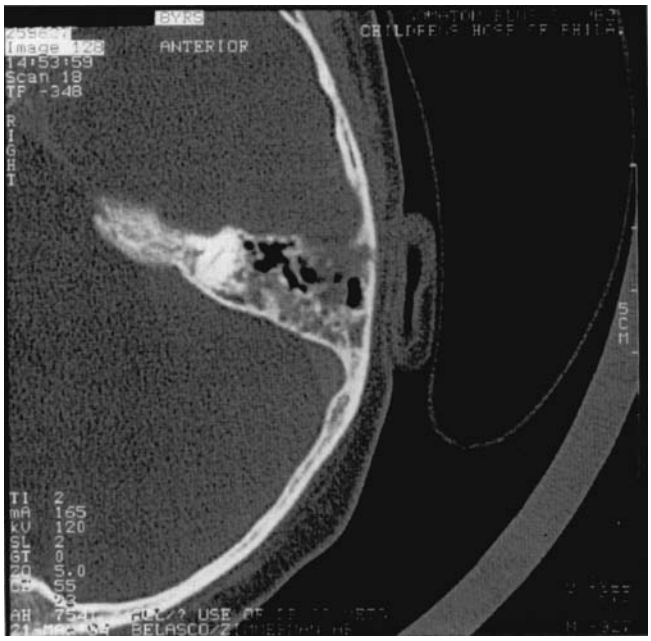

Fig. 6. CT after HBO therapy. Early remineralization of the area of necrosis. Air cells with bony walls are now apparent in the area of previous effacement.

0 value of 30% to a plateau of 80–85% of the level in non-irradiated tissues. They also showed that this effect is durable. Repeat irradiated tissue measurements in years 1, 2, and 3 remained elevated.

The second mechanism of action is stimulation of neovascularization. Using microangiographic techniques, greater numbers of blood vessels were seen in animals subjected to HBO following burns than in control animals not provided HBO [2–4].

Charles Scher, MD, PhD (Pediatric Oncologist)

What is the difference between "angiogenesis" and "neovascularization"?

Dr. Ashamalla. Angiogenesis indicates the de novo creation of vasculature in conjunction with fibroplasia stimulated by a high oxygen gradient. Neovascularization refers to capillary budding from pre-existing vessels in tissue adjacent to irradiated, hypovascular tissue [2].

Dr. Scher. Is the mechanism known; for example, is the angiogenesis growth factor implicated? If so, why do all the tissues in the body not share in the angiogenesis?

Dr. Womer. That question has been asked of experts, and no one really knows the answer.

Dr. D'Angio. Dr. Ames, you have had experience and training with HBO while in the Navy and have looked into the indications for HBO in medicine. Could you outline for us some of what are now considered to be the indications for instituting HBO? Please include in your discussion the risks involved and also the costs.

John W. Ames, MD (Resident, Radiation Oncology)

There are nearly a dozen clinical indications for HBO that are reimburseable by most third-party payers. They

include decompression sickness, carbon monoxide poisoning, and radionecrosis. I have recently completed a review of 151 patients coming to the University of Pennsylvania for HBO because of radiation therapy sequelae [5]. Nearly 80% of the patients with sufficient follow-up for analysis had complete resolution of their radiation-associated difficulties after having failed initial "standard" therapy, i.e., surgical debridement with or without antibiotics.

HBO is generally safe, but barotrauma to the sinuses, middle ear, and lungs can be a problem. Therefore, respiratory tract infections, hay fever allergy symptoms, asthma, or COPD are considered at least relative contraindications [6,7]. Additional albeit uncommon HBO risks include oxygen toxicity affecting the pulmonary and central nervous systems. The latter may become manifest as seizures. Myopia may also occur, but it is usually mild and reversible. Claustrophobia can be a problem, too, but is generally managed adequately with appropriate anxiolytic premedication.

With regard to cost, a course of HBO to treat radionecrosis is not inexpensive. It ranges between $10,000 and $30,000 [8]. However, compared to the overall average cost using surgery alone, the combination of both HBO and surgery costs about one-third as much, and results in an appreciably higher success rate.

Dr. D'Angio. Dr. Ames, how are the number of "dives" decided? Is the number used an arbitrary figure?

Dr. Ames. To a certain extent, yes. However, there is a large body of experience that indicates the present procedures are effective and the risks are small. The HBO protocol utilized here at Penn is based partly on the data generated by Roy Myers, Robert Marx, and others [1,3,6,9–12] demonstrating near-baseline transcutaneous oxygen measurements in irradiated tissues after approximately 20 dives as described earlier by Dr. Ashamalla.

Dr. Ashamalla. The role of HBO in the management of pediatric radiation-induced adversities has not been well studied. We reviewed the charts of 11 children who had had HBO following irradiation. Six of them had HBO for prophylaxis against osteoradionecrosis prior to orthodontal procedures, one for acute 8th cranial nerve palsy, and the rest for treatment of osteoradionecrosis. The treatments were tolerated very well. Two patients only had initial anxiety, nausea, and vomiting. The outcome of HBO treatment was excellent; every patient healed very well except for the patient with the 8th cranial nerve palsy. Two of the four children with osteoradionecrosis demonstrated new bone growth in follow-up CT scans. The child presented today continues to do well with no clinical evidence of recurrence or complications.

This case demonstrates that HBO is efficacious in the management of osteoradionecrosis—in this case of the mastoid region—and that it is well tolerated and safe.

Dr. Belasco. The discussions concerning HBO we had before deciding to use this method were very instructive.

We in pediatrics, unlike our counterparts dealing with the adult head and neck population, have had little experience with HBO except in large, deep soft tissue breakdown and infection. The concept of prophylaxis of potential problems—i.e., prevention of osteomyelitis, or meningitis—was a foreign concept to most of our consultants. I also think that most of us considered only the "HBO alone" data, which is obviously not so impressive as the results after combined modality care by which I mean HBO plus surgical debridement.

Although I preach that X-ray findings or laboratory test results without supporting clinical findings should not be given undue weight, this case shows there are always exceptions to the rule.

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SERIES EDITOR'S NOTE

Joseph Priestley (1733–1804) the discoverer of oxygen (Greek *oxys* = sharp, whence acidic + *-gen* from the root connoting birth) was an English phenomenon.

He was a theologian, educator, and scientist who made notable contributions in all these fields. His many books reflect a brilliant, innovative, and iconoclastic (Greek: *eikon* = image + *klast* = break) mind. It is interesting that he ended his days in Northumberland, Pennsylvania, where his home and laboratory is preserved as a museum.

Priestley trained for the Presbyterian ministry, but deviated from that orthodoxy (Greek *ortho* = straight, right + *doxa* = opinion) to Unitarianism. This religion (ultimately from Latin *legare* = to choose; whence *relegare* or to persist [in a belief]) stresses individuality in thought, belief, and action. As such, he opposed orthodoxy in its various guises (old German *wisa* = manner). He was, for example, against the English colonial policy of the time and against the trade in slaves (Latin *sclavus* = Slav, because this ethnic group was especially prone to enslavement in Central Europe in bygone times).[1] Priestley was protected by William Petty-Fitzmaurice (1737–1805) second Earl of Shelbourne for whose children Priestley had become tutor in 1772.[2] Notwithstanding this protection, his home and laboratory were wrecked by a mob because of Priestley's espousal of the French Revolution. He therefore emigrated to tolerant Pennsylvania in 1794, thus following his three sons who had preceded him to America in 1793.

While in England, he perfected the methods of studying gases and discovered ten new "airs" as they were called, including sulfur dioxide, ammonia [from Greek *Ammon,* the Egyptian god near whose temple the parent alkaline compound (Latin *sal ammoniacus* or salt of Ammon) was prepared], and "dephlogisticated air" (Greek from *phlox* = flame). *Phlogiston* = fire was thought to be a basic principle in itself. The connection with oxygen is obvious, and the *de-*(removal of) completes the rationale for Priestley's term. This research and his other interests brought him into contact with other luminaries, including John Adams, Thomas Jefferson, and Benjamin Franklin, a Pennsylvanian, who stimulated Priestley's studies of electricity. It was, however, another collaborator, Antoine L. Lavoisier (1743–1794), the great French scientist and discoverer of sulfur, who immediately grasped the importance and true nature of oxygen, the term he coined.[3] Priestley must have thought it a cruel and tragic perversion of his belief in the goals of the French Revolution when Lavoisier was guillotined during the Reign of Terror. Priestley became a respected member of the august Royal Society in 1766 as a result of his several accomplishments.

His fame preceded him when he emigrated to the New World, and he was offered the position of Professor of Chemistry at the University of Pennsylvania. He refused it, not wishing to lose independence of thought and action. He continued to pursue his several interests in Northumberland but nothing done in Pennsylvania attracted the same attention as his earlier work.

[1]The word appears to be the origin of the Italian greeting, "ciao," now almost universal. It is said by some to derive from the Genoese pronunciation and/or dialect of "schiavo" = slave, as in the once common salutation, "Your humble servent (or slave)."

[2]Another Pennsylvania connection: Landsdowne, PA is named after the country estate of this noble who became the Marquess of Landsdowne in 1784.

[3]*Coin* is from Latin *cuneum,* meaning *wedge,* which was the shape of the die used for stamping money. The verb form "to coin" has also come to mean minting a new word. *Mint* in this sense derives from Juno Moneta, in whose temple the Romans coined money and "moneta" is the term still used for "money" in Italian and—essentially—in Spanish (*moneda*).